Microbeam Radiation Therapy of Subcutaneous EMT-6 Mammary Carcinoma in Mice

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Introduction: Breast cancer is by far the most common cancer among females. It is reported that more than 30% of patients with breast cancer develop central nervous system metastasis; the median lifetime of breast cancer patients diagnosed with metastases is 3-9 months. Microbeam Radiation Therapy (MRT) has been shown to ablate 9L gliosarcoma in rat brain without major normal tissue damage. Mouse EMT-6 tumor model was used to evaluate the therapeutic effects of microbeams in this mammary carcinoma tumor model.

Methods and Materials: Small chunks of source EMT-6 tumors were transplanted subcutaneously into the calf area of the right hindleg of the mice. Three groups of mice were irradiated with single-fraction, unidirectional microbeams (90 μm in width, 300 μm center-to-center beam spacing), using an array size of 20 mm width. The in-slice entrance doses were 1612, 1687 and 1762 Gy for the first three groups. To simulate tissue depth in human irradiations, two additional groups were irradiated while positioned between two 5.1-cm acrylic slabs (one upstream and one downstream) at the doses of 800 and 837 Gy. The unirradiated control group included 8 mice. Tumors of different sizes were equally distributed to each group for consistency.

Results: All of the 8 mice in the control group had to be euthanized by the day 15 after irradiation because the size of the tumor exceeded 5% of their body weight. The following are the tumor ablation results and skin-damage outcome 24 days after the irradiations.

Group	Number of Mice	Use of plastic phantom	In-slice Dose (Gy)	Tumor ablation success	Tumor ablation success (%)
A	9	No	1612	7/9	78
B	8	No	1687	7/8	88
C	8	No	1762	8/8	100
D	7	Yes	800	4/7	71
E	7	Yes	837	7/7	100

The hair loss in the 1612-Gy group (Group A) was gradual, reaching 100% hair loss at day 18 of irradiation. No gross moist desquamation was observed in group A, although tissue shrinkage was exhibited in all mice in this and in all other groups. At the higher doses (Groups C, D, and E) the damage included moist desquamation, shrinkage, and fibrosis. Monte Carlo simulations of the microbeam dose distribution in tissue show that the radiation leakage between the microbeams (i.e., the “valley dose”) without the phantom is about 1.2% of the peak dose. As of the day 24, the irradiated legs are functional. Earlier mice experiments showed fast recovery from microbeam exposures. For the out-of-phantom irradiations, these included a significant hair re-growth for the 1550-Gy irradiations, and visible hair re-growth at 2000-Gy irradiations one month after the exposures. The hair in mice with 1550-Gy exposures has returned to almost normal density as of two months after the exposures. The 650-Gy, inside-phantom, microbeam-irradiated mice are recovering very much like the 1550-Gy outside-phantom mice. In contrast, single-fraction exposure of similar EMT-6 tumors to unsegmented, conventional broad beams from an x-ray machine (30 keV median energy) at 42 Gy, carried out by other investigators (Miura, Morris, Micca, et al., submitted for publication) as controls for a new treatment method, showed 80% tumor ablation. The tissue damage included severe shrinkage and fibrosis, and no hair re-growth was observed one year after the exposure.

Conclusions: Based on the above comparison of single-fraction microbeam and broad-beam exposures, we conclude that the unidirectional MRT has a larger therapeutic index (i.e., the ratio of the dose which produces an unacceptable level of normal tissue toxicity to that required for tumor control) than conventional, unsegmented beams. We note that the tumor-killing effect of the microbeams cannot be explained by the height of the valley dose, which was about 24 Gy in the mouse group with the highest microbeam dose.

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